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(54) Title: INHIBITION OF INTRAOPERATIVE MIOSIS/PRODUCTION OF MYDRIASIS BY CALCIUM CHANNEL BLOCKERS

(57) Abstract

This invention relates to a method for inhibiting intraoperative miosis or producing intraoperative mydriasis wherein a calcium channel blocker is introduced into an intraocular chamber of a subject undergoing intraocular surgery. Kits are provided for supplying the surgeon with an ophthalmologically-acceptable solution containing an effective amount of the calcium channel blocker.

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**INHIBITION OF INTRAOPERATIVE MIOSIS
/PRODUCTION OF MYDRIASIS
BY CALCIUM CHANNEL BLOCKERS**

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Field of the Invention

This invention relates to a method for inhibiting intraoperative miosis or producing intraoperative mydriasis, wherein a calcium channel blocker is introduced into an intraocular chamber of a subject undergoing intraocular surgery. Kits are provided for supplying the 10 surgeon with an ophthalmologically-acceptable solution containing an effective amount of the calcium channel blocker.

Background of the Invention

During intraocular surgery, particularly during the removal of the cataractous lens, a 15 small pupil in the operative eye can impair the work of the ophthalmic surgeon. A smaller pupil generally is found in older subjects, those individuals most frequently undergoing intraocular surgery. Moreover, the pupil becomes constricted or miotic when the eye is opened for surgery. Manipulation of intraocular instruments and the lens material is difficult when the pupil is miotic.

In order to maintain a desirable operative field during intraocular surgery, constriction 20 of the pupil should be prevented, inhibited or reversed or dilation of the pupil (mydriasis) should be accomplished. Mechanical devices for physically retracting the pupil during surgery have been proposed. See, e.g. U.S. Patents Nos. 4,991,567 and 4,782,820. Positioning of these devices, however, is time-consuming, and such devices are not suitable for many 25 intraocular surgical procedures involving delicate movements of instruments and tissues.

Pharmacological agents have been sought for inhibiting miosis or producing mydriasis. Before surgery, topical non-steroidal anti-inflammatory agents have been applied to prevent 30 intraoperative miosis, but this treatment is only minimally effective. (Keates et al Ann. Ophthalmol. 16(10) 919-921 (1984)) It is known that the pupil dilates during retrobulbar anesthesia but that this dilation is subsequently lost. During surgery, epinephrine has been added to intraocular irrigating solutions, but this drug does not often reverse miosis or produce mydriasis to a significant extent. Lotti (U.S. patent no. 5,153,205) teaches topical application

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of cholinergic M3 receptor antagonists to inhibit miosis. Nagy (U.S. patent no. 4,960,799) teaches topical administration of beta-blockers to treat inflammation of the eye and discloses that the beta-blockers also inhibit miosis during eye surgery. Bock et al. (U.S. patent no. 5,218,114) disclose that cholecystokinin antagonists may be used during intraocular surgery to prevent miosis.

The effectiveness of certain of the foregoing compounds for inhibiting miosis or producing mydriasis during intraocular surgery is not accepted by those skilled in the art. None are used universally.

Calcium channel blocking agents have been applied topically to the eye to reduce intraocular pressure and treat glaucoma. See, e.g., Abelson, U.S. patent no. 4,981,871. The use of an N-type and an L-type calcium channel blocker as an inhibitor of miosis also has been explored, but the results were not successful. (European Journal of Pharmacology, 209 (1991) 175-183). This study involved the use of δ -conotoxin, an N-type blocker, to block ruthenium red induced miosis. This toxin was successful in blocking the miosis induced by the ruthenium red; δ -conotoxin, however, is noxious and cannot be used therapeutically to treat miosis in the eye. Nifedipine, an L-type blocker, also was tested in this model, but was unable to block the miosis induced by the ruthenium red.

Summary of the Invention

It has been discovered that L-type calcium channel blockers inhibit miosis associated with intraocular surgery. This discovery is surprising in that an L-type calcium channel blocker was unable to block miosis associated with ruthenium red. As discussed in greater detail below, it is believed that ruthenium red acts through different pathways in causing miosis than the pathways responsible for miosis associated with intraocular surgery. The invention is believed to take advantage of this difference.

According to one aspect of the invention, a method for inhibiting intraoperative miosis or producing intraoperative mydriasis is provided. An effective amount of an L-type calcium channel blocker is introduced into an intraocular chamber of a subject, substantially simultaneously with performing intraocular surgery on the subject. Examples of L-type calcium channel blockers for use in the present invention are amlodipine, benedipine, bepridil, cinnarizine, cyclandelate, darodipine, diltiazem, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lidoflazine, manidipine, mepirodipine, nicardipine, nifedipine,

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niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, perhexiline, piperazine, prenylamine, tiamdipine, tiapamil, verapamil, analogs thereof and pharmacologically acceptable salts thereof. The preferred blocker is diltiazem.

In some embodiments, the L-type calcium channel blocker is introduced into the 5 intraocular chamber by instillation of a pharmacologically acceptable carrier containing said calcium channel blocker into the chamber. Preferably the L-type calcium channel blocker is introduced into the intraocular chamber by perfusing the chamber with an intraocular irrigating solution containing the blocker. The intraocular irrigation solution may contain the calcium channel blocker at a concentration of about 1 micromolar to 100 millimolar, but preferably at 10 0.1mM to 10.0mM. Most preferably, the intraocular irrigating solution contains diltiazem at a concentration of 0.1mM to 10mM.

The present invention also includes kits for intraocular surgery. In certain preferred 15 embodiments, the kits comprise a package including a first container containing a first amount of an ophthalmologically acceptable carrier, the first amount being between 10ml and 1000 ml. The package also includes a second container containing an L-type calcium channel blocker in 20 a concentrated amount. When the first amount is mixed with the concentrated amount to produce a therapeutic solution, the calcium channel blocker is present in the solution at a concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber.

In other preferred embodiments, the kit comprises a package including a first container 25 containing a first amount of an intraocular irrigation solution, wherein the solution is incomplete with respect to one or more irrigant components. The first amount is between 100ml and 1000ml. The package also includes a housing containing an L-type calcium channel blocker in a concentrated amount and containing said one or more irrigant components in a supplement amount. When the first amount is mixed with the concentrated amount and with 30 the supplement amount to produce a therapeutic solution, the calcium channel blocker is present in the solution at a concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber and said solution is pH and osmotically compatible with intraocular tissues. In this embodiment, the housing may be a second container containing both the L-type calcium channel blocker and the one or more irrigant components. The housing also can be a second and a third container, the second container containing the calcium channel blocker and the third container containing the one or

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more irrigant components.

The kits of the invention may include, in addition, instructions for preparation of the therapeutic solution and for use of the solution in connection with intraocular surgery, and in particular to inhibit miosis or produce intraoperative mydriasis during intraocular surgery.

5 The intraocular solutions used in the invention are water solutions containing irrigant components preferably selected from members of the group consisting of sodium ions, potassium ions, calcium ions, magnesium ions, chloride ions, acetate ions, dibasic phosphate ions, bicarbonate ions, citrate ions, dextrose and glutathione disulfide.

10 The present invention also sets forth a device comprising a bottle containing an intraocular solution and an L-type calcium channel blocker present in an amount effective for inhibiting miosis when perfused or instilled into an intraocular chamber of an eye during intraocular surgery. The bottle contains between 10ml and 1000ml of the intraocular solution and the calcium channel blocker, preferably at a concentration between 0.1mM and 10mM. 15 The intraocular solution is ophthalmologically acceptable, including being pH compatible and iso-osmotic with the eye.

Other features and advantages of the invention will be apparent from the following description and from the claims.

Brief Description of the Drawings

20 Figure 1 is a graph illustrating the effect on pupil size of intraocular perfusion with an irrigant containing 100 μ M of the calcium channel blocker diltiazem.

Figure 2 is a graph illustrating the effect on pupil size of intraocular perfusion with an irrigant containing 1mM of the calcium channel blocker diltiazem.

25 Figure 3 is a graph illustrating the effect on post-operative intraocular pressure following intraocular perfusion with an irrigant containing 100 μ M diltiazem.

Figure 4 is a graph illustrating the effect on post-operative pupil size following intraocular perfusion with an irrigant containing 100 μ M diltiazem.

Figure 5 is a graph illustrating the effect on post-operative intraocular pressure following intraocular perfusion with an irrigant containing 1 mM diltiazem.

30 Figure 6 is a graph illustrating the effect on post-operative pupil size following intraocular perfusion with an irrigant containing 1 mM diltiazem.

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Detailed Description of the Invention

This invention encompasses methods for inhibiting intraocular surgical miosis or producing intraoperative mydriasis by delivering L-type calcium channel blockers to an intraocular chamber of an eye undergoing surgery. Intraoperative miosis and surgical miosis are used interchangeably herein. Miosis means the constriction of the pupil. Miosis occurs during standard intraocular operative procedures which involve mechanical contact with ocular tissue and manipulation of ocular components. The resultant small pupil size hinders the view of the surgeon, minimizes access to the intraocular cavity and may force modification of the surgical technique. Inhibition of miosis is achieved by preventing, inhibiting or reversing the iris muscle contraction which causes a small pupil during intraocular surgery.

Mydriasis is an abnormal dilation of the pupil. Mydriasis can be useful intraoperatively by maximizing access to the intraocular cavity.

It has been discovered that L-type calcium channel blockers are capable of inhibiting intraocular surgical miosis or producing intraoperative mydriasis when applied to an intraocular chamber substantially simultaneously with surgery. While not limiting the treatment of this invention to the validity of one proposed mechanism of action, it is believed that the L-type calcium channel blockers, when introduced into an intraocular chamber, decrease the ability of the iris to contract by blocking the neuronal conduction of electrical impulses by nerves within the eye, presumably in communication with the iris.

It was known that ruthenium red can cause miosis and that this miosis was blocked by δ -conotoxin but not nifedipine. δ -conotoxin is an N-type calcium channel blocker while nifedipine is an L-type. Ruthenium red is a noxious unnatural substance which is added exogenously to the eye to induce these changes. Its mechanism of action in causing miosis is unknown, and ruthenium induced miosis very well may result from effects unrelated to nerve transmission. We believe that surgically induced miosis and ruthenium red induced miosis involve different pathways. Calcium channels are of several types, L, N, P and T. These types have varying degrees of specificity for various drugs, with different drugs acting on different channels. They are believed to be involved in different neuronal functions. The present invention involves the discovery that blockers of one such type of calcium channel, the L-type, can prevent, inhibit and even reverse the miosis induced by mechanical trauma to the eye during the course of eye surgery, even though one such blocker was shown in the prior art to be ineffective in stopping miosis induced using ruthenium red.

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Intraocular chamber means a space within the eyeball which is bordered by characteristic tissues forming an identifiably separate region. The eye is comprised of three chambers: the anterior chamber, the posterior chamber and the vitreous chamber. In the method of the present invention wherein L-type calcium channel blockers are introduced into an intraocular chamber to inhibit miosis, it is believed important that the calcium channel blocker contact the nerves that activate the iris reflex. Although it is believed that the nerves activating iris contraction reside mainly in the tissue surfaces of the anterior and posterior chamber, they may travel as well to more remote intraocular surfaces such as those defining the vitreous chamber. In the present invention, the L-type calcium channel blockers preferably are brought into contact with tissues forming the anterior and posterior chamber surfaces.

The method of the invention is for treatment of surgical miosis or for producing intraoperative mydriasis in eyes of mammalian subjects (e.g., humans, nonhuman primates, dogs, cats, horses, sheep, goats, cows, pigs and rodents). Surgical procedures for which this invention is useful include, but are not limited to, the manipulation or the removal of the cataractous lens, phacoemulsification, the manipulation, insertion and/or removal of a prosthetic intraocular lens, pars plana vitrectomy, vitreal surgery, retinal surgery, extracapsular or intracapsular cataract extraction/lens aspiration and anterior segment reconstruction.

The compounds useful in practicing this invention are L-type calcium channel blockers. The term L-type "calcium channel blockers" defines a class of molecules well known to those of ordinary skill in the art. They include compounds which have been shown to prevent or delay the cardiac contracture which is caused by an accumulation of intracellular calcium. They also include compounds which have been shown to block the inward movement of extracellular Ca^{++} into a responsive cell. The term is equivalent to the terms "compound having L-type calcium channel blocking activity" or "calcium channel antagonist of the L-type".

Without limiting the invention to the specific compounds listed, the following is a list of representative L-type calcium channel blockers useful in this invention: amlodipine; benedipine; bepridil; cinnarizine; cyclandelate; darodipine; diltiazem; etafenone; felodipine; fendiline; flunarizine; gallopamil; isradipine; lacidipine; lidoflazine; manidipine; mepirodipine; nicardipine; nifedipine; niludipine; nilvadipine; nimodipine; nisoldipine; nitrendipine; perhexiline; piperazine; prenylamine; tiamdipine; tiapamil; verapamil; analogs thereof and pharmacologically acceptable salts thereof. The preferred calcium channel blocker is diltiazem

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and its pharmacologically acceptable salts.

Verapamil and the like are disclosed in U.S. patents 3,261,859, 4,593,042 and 4,681,970. Nifedipine is disclosed in U.S. patent 3,485,847 and is a 1,4-dihydropyridine in which the 2 and 6 positions are substituted by methyl groups, the 4- position by 2-nitrophenyl and the 3 and 5 positions by carboxylic acid methyl ester groups. Similar compounds are disclosed in U.S. patent nos. 3,455,945, 3,325,505 and 3,441,468 to Leow and 3,470,297 and 3,511,837 to Bossert, which introduced variations in the 4-substituent. U.S. patent nos. 3,905,970 to Bossert, et al. and 3,985,758 to Marakami et al. introduced certain mono- or dialkylamino-alkylene and nitrogen-containing heterocyclic alkylene groups into one or both of the 3,5 ester groups. U.S. Patent No. 4,307,103 and 4,393,070 to Sato disclose 1,4-dihydropyridines in which the 2 position is not substituted by alkyl, but instead is substituted with cyano, formyl or certain other substituents and the ester group in the 3 position may contain various substituted alkyl groups including substituted alkylaminoalkyl, heterocyclic aminoalkyl and aroylaminoalkyl, including phthalminidoethyl. U.S. Patent No. 4,448,964 to Muto et al. discloses compounds in which the 3-position ester group contains certain substituted piperidinyl alkylene groups.

Other pyridine compounds having calcium channel blocking activities are disclosed in U.S. Patents 4,652,573, 4,755,512, 4,791,117, 4,794,187, 4,814,455, 4,829,076, 4,871,745, 4,895,846 and 4,912,223.

Diltiazem and analogs are disclosed in U.S. patents 3,562,257 and 4,552,695.

Analogs of the foregoing compounds that function as L-type calcium channel blockers also are specifically intended to be embraced by this invention. An analog is a molecule that is structurally similar to the parent molecule and is capable of achieving the same or substantially the same function or activity in terms of miosis or mydriasis. The ability of such analogs to prevent, inhibit or reverse surgical miosis or produce intraoperative mydriasis according to the invention can be tested easily using no more than routine experimentation.

Pharmaceutically acceptable salts of L-type calcium channel blockers include the conventional non-toxic salts formed from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, maleic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic,

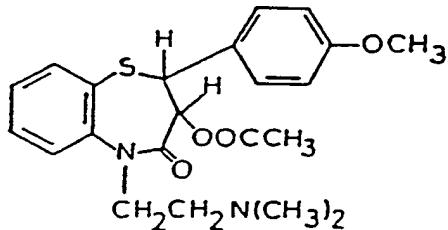
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salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, formic, malonic, naphthalene-2-sulfonic, benzenesulfonic and the like.

5 The structure of the preferred calcium channel blocker utilized in the method and compositions of this invention is as follows:

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Diltiazem

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The chemical name of diltiazem (d-diltiazem) is (2S,3S)-3-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-(methoxyphenyl))-1,5-benzothiazepin-4(5H)-one hydrochloride. The chemical name of the l-enantiomer of diltiazem is (2R,3R)-3-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4(methoxyphenyl)-1,5-benzo-thiazepin-4(5H)-one hydrochloride.

20 Analogs of diltiazem include: 1,3,4,5-tetrahydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one; 1,3,4,5-tetrahydro-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one; 1,3,4,5-tetrahydro-hydroxy-4-(4-methoxycarbonyl)-2H-1-benzazepin-2-one; *trans*-1,3,4,5-tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one; *cis*-3-hydroxy-1-25 [2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one, monohydrochloride; *cis*-3-(acetoxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one, monohydrochloride; 1,3,4,5-tetrahydro-3-methyl-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one; 30 *cis*-1,3,4,5-tetrahydro-3-methyl-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one; *cis*-3-methyl-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2H-1-benzazepin-2-one, monohydrochloride;

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1,3,4,5-tetrahydro-2-(4-methoxyphenyl)-3-methyl-4-oxo-1,5-benzothiazepine-3-carboxylic acid, methyl ester; 1,3,4,5-tetrahydro-2-(4-methoxyphenyl)-3-methyl-
4-oxo-1,5-benzothiazepine-3-carboxylic
acid; *cis*-2,3-dihydro-2-(4-methoxyphenyl)-3-methyl-1,5-
5 benzothiazepin-4(5H)-one; *cis*-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-
(4-methoxyphenyl)-3-methyl-1,5-benzothiazepin-4(5H)-one hydrochloride;
3-hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-
1,5-benzothiazepine-4(5H)-one hydrochloride;
3-hydroxy-2,3-dihydro-5-[2-(methylamino)ethyl]-2-(4-methoxyphenyl)-
10 1,5-benzothiazepine-4(5H)-one hydrochloride; 3-hydroxy-2,3-dihydro-
5-[2-(dimethylamino)ethyl]-2-(4-hydroxyphenyl)-1,5-benzothiazepine-4(5H)-one hydrochloride;
3-hydroxy-2,3-dihydro-5-[2-(methylamino)ethyl]-2-
(4-hydroxyphenyl)-1,5-benzothiazepine-4(5H)-one hydrochloride; 3-acetoxy-8-chloro-
2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5)-one
15 maleate (1:1).

The L-type calcium channel blockers are introduced into an intraocular chamber in ophthalmologically acceptable amounts and in ophthalmologically acceptable solutions. Such amounts and solutions are those that cause no medically unacceptable side-effects when administered to an intraocular chamber of the eye according to the methods described herein.
20 Preferred ophthalmologically acceptable solutions are sterile solutions which are approximately iso-osmotic with respect to the fluid in intraocular chambers. Such solutions are non-irritating to the eye and maintain the osmotic stability of the tissues defining the chamber. The osmolality preferably is between about 250 and about 350 mOsm and most preferably about 280-320 mOsm. The solutions also are pH compatible with the environment of the selected intraocular chamber. The pH of the solution preferably is between about 6.5 and about 8.0 and more preferably between about 7.2-7.8. Most preferably the pH is 7.4. The solutions optionally contain particular buffering agents and other factors to support metabolism of the eye tissue. For example, the solution may contain bicarbonate at a concentration of between about 10 and 50 mM/l. The solution also may contain, for example, dextrose (D-glucose) and glutathione. The buffer preferably is a phosphate buffer whereby the final phosphate concentration is between about 1 and 5 mM/l. Other additives include sodium and potassium salts such as sodium and potassium chlorides, sulfates, acetates, citrates, lactates, and

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gluconates. Calcium and magnesium chlorides also may be added.

The L-type calcium channel blocker is introduced into the intraocular chamber in an ophthalmologically acceptable carrier solution containing the calcium channel blocker at an effective concentration for inhibiting surgical miosis or producing intraoperative mydriasis.

5 Introduced into the chamber means instilling it in the chamber or perfusing it in the chamber. The solution containing the calcium channel blocker can be instilled in an intraocular chamber using a syringe at a time prior to the start of surgery or very early in the procedure. This instillation may be a single application of a small amount of carrier solution containing the calcium channel blocker. When instilled in an intraocular chamber prior to surgery, the L-type 10 calcium channel blocker is intended to exert its effect for the total time anticipated for the surgical procedure. The solution thus contains amounts of an L-type calcium channel blocker sufficient to assure persistent inhibition of miosis or continuous mydriasis during the surgery. The solution also may be instilled into the chamber as a "wash", once or several times during the surgery.

15 The eye also may be perfused during the course of the surgery with an ophthalmologically acceptable irrigation solution containing the L-type calcium channel blocker. Perfusion is accomplished by means of a perfusing needle, cannula or probe which delivers in a sterile manner perfusing solution from a container. The cannula (as generally used in intraocular surgery) is capable of both providing the irrigation solution to the eye and also 20 aspirating fluid thereby maintaining a clear field of operation for the surgeon.

The duration of action of the L-type calcium channel blocker can influence the time at which the blocker is introduced into a chamber of the eye undergoing surgery. It is intended that the L-type calcium channel blocker be applied substantially simultaneously with the surgical procedure. "Substantially simultaneously" means that the blocker is introduced such 25 that its effect coincides with the time during which the surgical procedure is being performed.

The duration of action of the blocker will affect the choice of the blocker and the method by which the blocker is introduced into the intraocular chamber. Thus, an L-type calcium channel blocker which is capable of exhibiting an effect for about a half hour or more (i.e., the entire time which may be needed to perform the eye surgery) may be introduced into 30 an intraocular chamber in a single dose prior to or at the beginning of surgery. Those L-type calcium channel blockers that have a somewhat shorter duration of action may need re-instillation, such as by a wash. In a preferred embodiment, however, the blockers have a

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short duration of action and are introduced into the intraocular chamber by constant perfusion of an intraocular chamber during the course of surgery.

The L-type calcium channel blockers of the invention are applied in effective amounts. An effective amount is that amount which prevents, inhibits or reverses miosis or produces mydriasis to a medically useful extent during intraocular surgery, (e.g. the operative field is improved for the surgeon or it is easier for the surgeon to manipulate surgical instruments and intraocular tissues). An effective amount is one controlled by a number of factors, including: the subject; the inherent anti-miotic or mydriatic activity of the L-type calcium channel blocker; the amount of the L-type calcium channel blocker used; its duration of action; and the method by which it is introduced into the intraocular chamber, i.e., whether by a single application or by continuous perfusion. A perfusion solution having between 1 micromolar to 100mM of L-type calcium channel blocker is believed to deliver an effective amount during intraocular surgery. Preferably perfusion solutions contain between 0.1mM to 10mM blocker. It is important that the L-type calcium channel blockers do not produce, at effective concentrations, long-term deleterious changes in the eye nor cause inflammation, discomfort or irritation. The determination of an effective dose for any selected compound is well within the level of ordinary skill in the art.

The present invention also includes kits providing an L-type calcium channel blocker and a carrier for introducing the blocker into an intraocular chamber during surgery. A carrier is an ophthalmologically acceptable solution in which the blocker is dissolved prior to application to an intraocular chamber. It is important that any solution applied to an intraocular cavity be free of any factors that would injure intraocular tissue. Thus it preferably is sterile, approximately iso-osmotic, at the correct pH and contains factors to support metabolism in the tissue, as described above.

The long-term effects of storage on the stability of L-type calcium channel blockers that contain, for example, an ester function within the structure are believed to be problematic, particularly when the blockers are in aqueous solutions at neutral or alkaline pH. Accordingly, it is an aspect of the invention that kits be provided for preparation of therapeutic solutions containing an L-type calcium channel blocker within hours of surgery. In these kits, the blockers can be in a stable powdered form or in a stable concentrated form such as concentrated in an acidic solution. The powdered or concentrated L-type calcium channel

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blocker then can be dissolved or diluted in the ophthalmologically acceptable carrier solution immediately in advance of surgery.

The kits comprise a package, such as a box, blister pack or similar packing vehicle used conventionally to hold containers of liquid. The package may be coated with an impervious cover to assist in protecting the sterility of the contents during transport and storage. In the package are a container containing an amount of a carrier solution (or components thereof) and one or more containers containing an L-type calcium channel blocker and any components missing from the carrier solution. The containers preferably are glass bottles, but may be formed of any inert material such as a rigid or flexible plastic in the form of bottles or bags that allow transport and storage of liquid without loss of fluid or contamination of the contents.

In certain preferred embodiments, the containers may be chambers in a single housing. In these embodiments the container may comprise in addition a structure to permit communication of the contents of the chambers without opening the container. In one such embodiment, the blocker and the ophthalmologically acceptable carrier solution can be supplied in separate chambers of a two-chamber vial. Communication between the chambers can be provided by a frangible membrane. In use, the membrane is pierced or ruptured, with the carrier solution flowing into the chamber containing the blocker (or vice versa). The blocker, in powdered form or in a concentrated form, then is dissolved or diluted into the solution. In another embodiment, the upper and lower chambers are constructed and arranged within a syringe. Movement of the plunger causes the contents of the two chambers to mix.

In one aspect of the invention, the kit may be used to provide a carrier solution for instilling a single amount or wash amounts of an L-type calcium channel blocker into an intraocular chamber. In these embodiments, the containers for the carrier solution preferably includes about 10ml to about 50ml of carrier solution. The container may be a bottle or vial with piercable septum. The blocker may be supplied for example in a stable, concentrated solution (also in a bottle or vial with a piercable septum). In use, the septum of the bottle or vial containing the calcium channel blocker is pierced by the needle of a syringe and transferred to the bottle or vial containing the carrier solution. An ophthalmologically acceptable solution of predetermined blocker concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber is thereby formed. The solution then may be removed by syringe from the vial and instilled into the intraocular chamber.

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In another aspect of the invention, the kit may be used to provide a carrier for perfusing an L-type calcium channel blocker into an intraocular chamber during eye surgery. In these embodiments, the first container contains an intraocular irrigation solution (or components thereof) in an amount from about 100ml to 1000ml, preferably about 500ml. Most preferably the first container is a bottle having a rubber septum which can be punctured by a needle attached to a tube for delivering the contents of the container to a perfusing needle and hence to the eye. Another container(s) includes a predetermined amount of an L-type calcium channel blocker, and, in certain embodiments, components of the intraocular irrigation solution. The contents of the containers are mixed in a manner that maintains sterility to form an ophthalmologically acceptable solution containing the blocker at a concentration effective for inhibiting surgical miosis when perfused into an intraocular chamber during surgery.

As mentioned above, the solution contained in the first container may be only components of an intraocular irrigation solution. In other words, the intraocular irrigation solution may be "incomplete". One or more components of the intraocular irrigation solution may be provided in a second container with the blocker or separately in a different container. Such arrangements can serve dual purposes. Firstly, certain components of the intraocular irrigation solution, such as organic components, may be more stable at pHs other than physiological intraocular pH. Thus, as with the blocker, the separation of such one or more components from the irrigation solution (and the calcium blocker solution) until the time of mixing just prior to surgery permits long term storage. Secondly, by providing important components in separate containers, a package may be constructed and arranged whereby an ophthalmologically acceptable irrigation solution is created only when all of the various contents of the different containers are mixed together. In this manner, the surgeon or medical staff supporting the surgeon will be inclined to use the materials as directed as opposed to substituting other materials which may not be as clinically desirable.

Thus, in certain preferred embodiments of the kit of the invention, the package includes a first container containing between 100ml and 1000ml of an intraocular solution, wherein the solution is incomplete with respect to one or more solution components. The package also includes a second container containing an L-type calcium channel blocker and a third container containing said one or more solution components. In these embodiments, the contents of the first, second, and third containers are mixed together to form a solution which is pH and osmotically compatible with the intraocular environment of an eye and in which the blocker is

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present at a concentration effective for inhibiting surgical miosis when introduced into an intraocular chamber.

Examples of suitable intraocular irrigation solutions are RINGERS solution, balanced salt solution and glutathione-bicarbonate-RINGERS solution. The preferred compositions and methods of preparation of suitable irrigation solutions have been disclosed in U.S. patent numbers 4,550,022 and 4,443,432 to Garabedian which are hereby incorporated by reference.

The kits may include instructions for preparation of a carrier or irrigation solution. The instructions may detail the use of the L-type calcium channel blocker or solution in an intraocular chamber in connection with inhibiting surgical miosis. They also may include useful additional implements for mixing the contents of the containers in the kits or for delivery of the final therapeutic solution to an intraocular chamber.

The present invention also sets forth a device comprising a bottle, such as a wash bottle or an irrigation bottle, containing an intraocular irrigation solution including an L-type calcium channel blocker present in an amount effective for inhibiting miosis or producing mydriasis when instilled into an intraocular chamber of an eye during intraocular surgery. The bottle preferably is formed from glass, but may also be rigid or flexible plastic and may be a bag. The device is useful for instilling or perfusing a solution in an intraocular chamber during surgery. A bottle suitable for wash or injection preferably contains 10ml to 50ml of the ocular irrigating solution and preferably contains the blocker at a concentration between about 0.1mM and 10mM. A bottle suitable for use in perfusion of an intraocular cavity contains at least 100 ml of the intraocular irrigation solution and preferably contains the blocker at a concentration between about 1 micromolar to 10mM.

Example 1

Lens removal surgery in dogs. All dogs underwent a presurgical work up including a complete physical exam, a complete ocular exam, an intraocular pressure measurement and a pupil measurement using a hand-held caliper (measured to the nearest millimeter).

The dogs were treated with the following anti-inflammatory regimen: on the morning before surgery, the dogs were given .5 mg/lb prednisone PO, one drop of .1% dexamethazone with neomycin and polymixin B (AK-Trol™) and .25 mg/lb flunixin meglumine IV. Beginning one hour before surgery, and every 15 minutes thereafter up until surgery, one drop of AK-Trol was applied topically. Post-operatively, QID one drop .1% AK-Trol Sx day. This was repeated at 1, 2 and 3 days post-operatively.

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Surgical removal of the lens was performed using the techniques of phacoemulsification in mongrel dogs of either sex. General anesthesia was induced by intravenous Pentothal (25mg/ml, at a dose of 8mg/lb) and maintained by inhalation with isoflurane. The surgical site was prepared, draped and washed with BETADINE. Surgery was performed on one eye, then the other. Lactated RINGERS solution was administered IV during the procedure, 4ml/lb/hr.

The surgical procedure was performed by observation through a surgical microscope. The anterior chamber was entered at the limbus and an anterior capsulotomy was performed. Using the phacoemulsification probe and irrigation/aspiration, the lens content material was broken up and removed from the eye. The irrigation solution was a balanced salt solution containing either the drug substance or a vehicle control. Over 15-20 minutes of surgical time, 100-400 mls of irrigation solution were delivered. Pupil size was monitored under the surgical microscope with the hand-held caliper.

At the end of surgery, the eye was closed with sutures and surgery on the other eye was performed similarly. When the second procedure was completed, the animal was allowed to recover. Post-operative inflammation was measured with a KOWA™ Flarmeter for 72 hours after surgery.

Following the foregoing protocol, three dogs were treated in one eye with a vehicle and in the other eye with a perfusion solution containing 100 micromolar diltiazem. The results are shown in Fig. 1 and TABLE 1, which demonstrates that pupil size was increased only slightly between the 10 and 20 minute interval after the initiation of the surgical procedure. (The perfusion solution was applied beginning at seven minutes.) The results were as follows:

TABLE 1
Pupil Diameter (mm)

	<u>Time (minutes)</u>	<u>Diltiazem (100μM)</u>	<u>Placebo</u>
	Pre-Operative	8.67	8.67
	Post-Anesthesia	3.00	3.17
	0	3.67	3.75
30	5	3.13	4.56
	10	6.20	3.88
	15	5.75	5.30
	20	5.93	5.40
	25		
35	Post-Closure	4.42	4.42

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Example 2

The protocol of Example 1 was followed, except that three dogs were treated in one eye with a vehicle and in the other eye with a perfusion solution containing 1 millimolar diltiazem. As demonstrated in Fig. 2 and TABLE 2, the eye receiving the 5 diltiazem had a pupil size substantially greater than the eye receiving the placebo. The results were as follows:

TABLE 2
Pupil Diameter (mm)

	<u>Time (minutes)</u>	<u>Diltiazem (1mM)</u>	<u>Placebo</u>
	Pre-Operative	9.00	9.00
	Post-Anesthesia		
10	0	3.50	4.00
15	5	4.50	3.63
	10	9.20	4.30
	15	8.33	4.75
	20	10.75	3.00
	25	9.63	4.17
20	Post-Closure	9.33	3.83

Example 3

The effect 100 μ M of diltiazem on post-operative intraocular pressure (IOP) was measured. No statistical differences were apparent between the eyes treated with 25 100 μ M diltiazem and the eyes treated with the placebo. The results are shown in Fig. 3.

Example 4

The effect of 100 μ M diltiazem on post-operative pupil size also was measured. No statistical differences were observed in eyes treated with 100 μ M diltiazem versus 30 eyes treated with placebo through 72 hours post-operatively. The results are shown in Fig. 4.

Example 5

The effect of 1mM diltiazem on post-operative intraocular pressure (IOP) was 35 measured. No statistical differences were apparent between the eyes treated with 1mM diltiazem and the eyes treated with the placebo. The results are shown in Fig. 5.

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Example 6

The effect of 1mM diltiazem on post-operative pupil size also was measured. No statistical differences were observed in eyes treated with 1mM diltiazem versus eyes treated with placebo through 72 hours post-operatively. The results are shown in Fig. 6.

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While the invention has been described in terms of preferred embodiments, those of ordinary skill in the art will recognize that modifications and equivalents may be made without departing from the scope of the present invention which is limited only by the following claims:

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CLAIMS

1. A method for inhibiting intraoperative miosis or producing intraoperative mydriasis comprising introducing into an intraocular chamber of a subject, substantially simultaneously with performing intraocular surgery on said subject, an amount of an L-type calcium channel blocker effective for inhibiting surgical miosis or producing intraoperative mydriasis.
5
2. The method of claim 1 wherein said L-type calcium channel blocker is selected from the group consisting of amlodipine, benedipine, bepridil, cinnarizine, cyclandelate, darodipine, diltiazem, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lidoflazine, manidipine, mepirodipine, nicardipine, nifedipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, perhexiline, piperazine, prenylamine, tiamdipine, tiapamil, verapamil, analogs thereof and pharmacologically acceptable salts thereof.
10
3. The method of claim 1 wherein said L-type calcium channel blocker is introduced into said intraocular chamber by perfusing said chamber during intraocular surgery with an intraocular irrigating solution containing said blocker.
15
4. The method of claim 2 wherein said L-type calcium channel blocker is introduced into said intraocular chamber by perfusing said chamber during intraocular surgery with an intraocular irrigating solution containing said L-type calcium channel blocker.
20
5. The method of claim 1 wherein said L-type calcium channel blocker is introduced into said intraocular chamber by injection of a pharmacologically acceptable carrier containing said L-type calcium channel blocker into said intraocular chamber.
25
6. The method of claim 2 wherein said L-type calcium channel blocker is introduced into said intraocular chamber by injection of a pharmacologically acceptable carrier containing said L-type calcium channel blocker into said intraocular chamber.
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7. The method of claim 3 or 4 wherein said L-type calcium channel blocker is diltiazem, an analog of diltiazem, or pharmacologically acceptable salts thereof.

8. The method of claim 3 or 4 wherein said L-type calcium channel blocker is at a concentration of 1 micromolar to 100mM in said intraocular irrigating solution.

9. The method of claim 5 or 6 wherein said L-type calcium channel blocker is at a concentration of 0.1mM to 10mM in said carrier.

10. 10. A kit for intraocular surgery comprising a package including:

a. a first container containing a first amount of an ophthalmologically acceptable carrier, the first amount being between 10ml and 1000ml; and

b. a second container containing an L-type calcium channel blocker in a concentrated amount,

wherein when the first amount is mixed with the concentrated amount to produce an ophthalmologically acceptable solution, the L-type calcium channel blocker is present in said ophthalmologically acceptable solution at a concentration effective for inhibiting intraoperative miosis or producing intraoperative mydriasis when perfused in an intraocular chamber.

11. 11. A kit for providing an irrigant for intraocular surgery comprising a package including:

a. a first container containing an irrigation amount of an intraocular irrigation solution, wherein the solution is incomplete with respect to one or more irrigant components, the irrigation amount being between 100 ml and 1000 ml; and

b. a housing containing an L-type calcium channel blocker in a concentrated amount and containing said one or more irrigant components in a supplement amount;

30 wherein, when the irrigation amount is mixed with the concentrated amount and with the supplement amount to produce an ophthalmologically acceptable solution, the L-type calcium channel blocker is present in said ophthalmologically

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acceptable solution at a concentration effective for inhibiting intraoperative miosis or producing intraoperative mydriasis when perfused into an intraocular chamber during intraocular surgery, and said ophthalmologically acceptable solution is pH and osmotically compatible with intraocular tissues.

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12. A kit for producing an irrigant for intraocular surgery as claimed in claim 11, wherein said housing is two containers, a second container containing said one or more irrigant components in the supplement amount; and a third container containing the L-type calcium channel blocker in the concentrated amount.

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13. The kit of claims 10, 11 and 12 further comprising instructions for preparation of said ophthalmologically acceptable solution and for use of said ophthalmologically acceptable solution as an irrigant during intraocular surgery.

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14. The kit of claims 10, 11 and 12 wherein said ophthalmologically acceptable solution is a water solution containing components selected from members of the group consisting of sodium ion, potassium ion, calcium ion, magnesium ion, chloride ion, acetate ion, dibasic phosphate ion, bicarbonate ion, citrate ion, dextrose and glutathione disulfide, said solution being adjusted to a pH of between 6.5 and 8.

20

15. The kit of claims 10, 11 and 12 wherein said L-type calcium channel blocker is selected from the group consisting of amlodipine, benedipine, bepridil, cinnarizine, cyclandelate, darodipine, diltiazem, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lidoflazine, manidipine, mepirodipine, nicardipine, nifedipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, perhexiline, piperazine, prenylamine, tiamdipine, tiapamil, verapamil, analogs thereof and pharmacologically acceptable salts thereof.

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16. The kit of claim 15 wherein said L-type calcium channel blocker is diltiazem, an analog of diltiazem, or pharmacologically acceptable salts thereof.

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17. A device comprising a bottle containing an intraocular irrigating solution and an L-type calcium channel blocker present in an amount effective for inhibiting miosis or producing intraoperative mydriasis when perfused into an intraocular chamber of an eye during intraocular surgery.

5

18. The device claimed in claim 17 wherein said bottle contains at least 100ml of said intraocular irrigating solution.

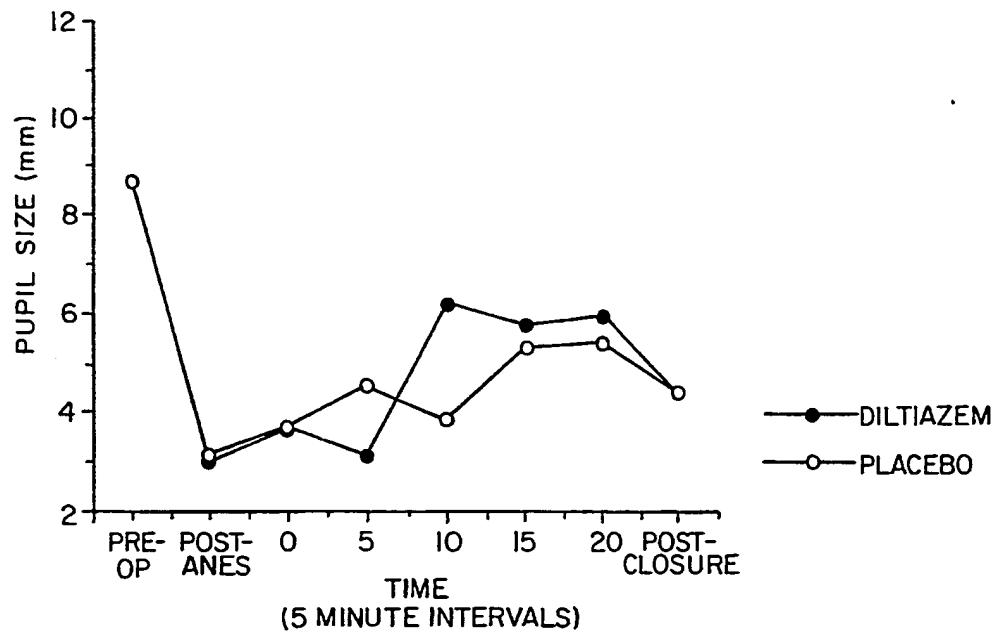
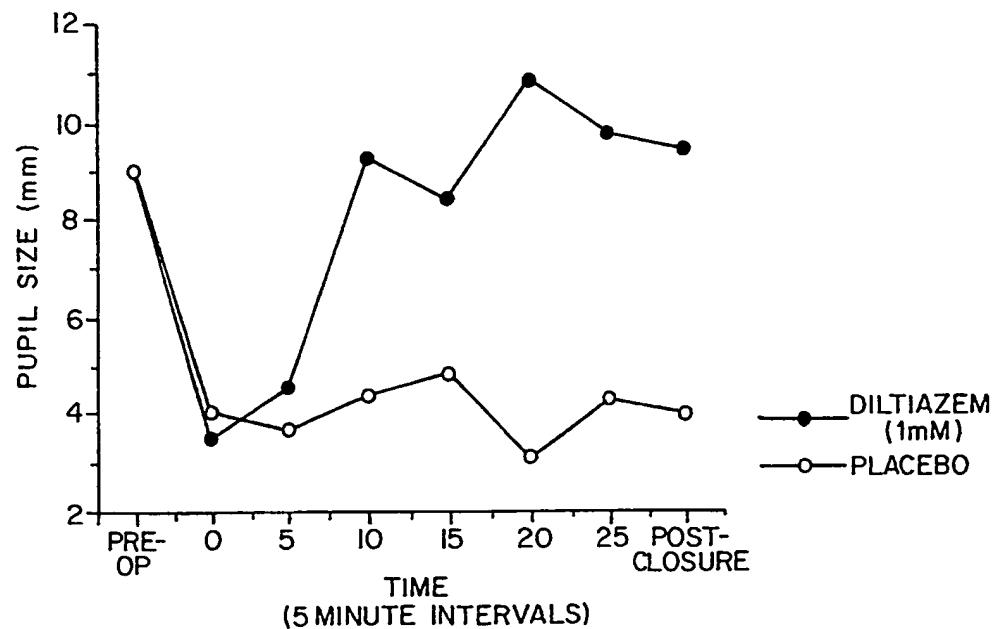
19. The device of claim 18 wherein said bottle contains an L-type calcium channel blocker at a concentration between 0.1mM and 10mM.

10 20. The device of claim 19 wherein said L-type calcium channel blocker is diltiazem, an analog of diltiazem, or pharmacologically acceptable salts thereof.

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*Fig. 1**Fig. 2*

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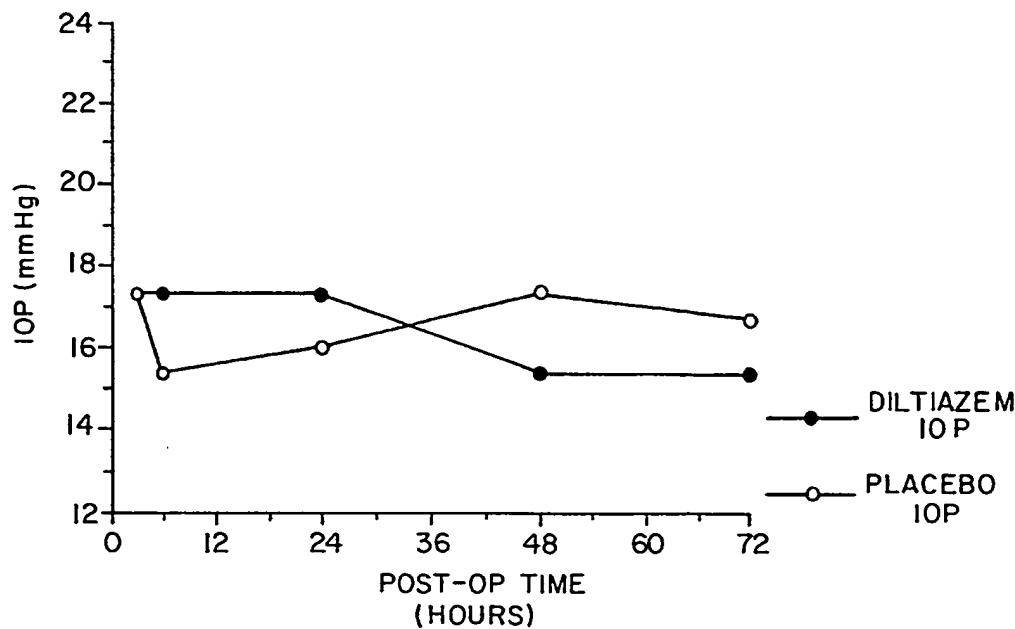
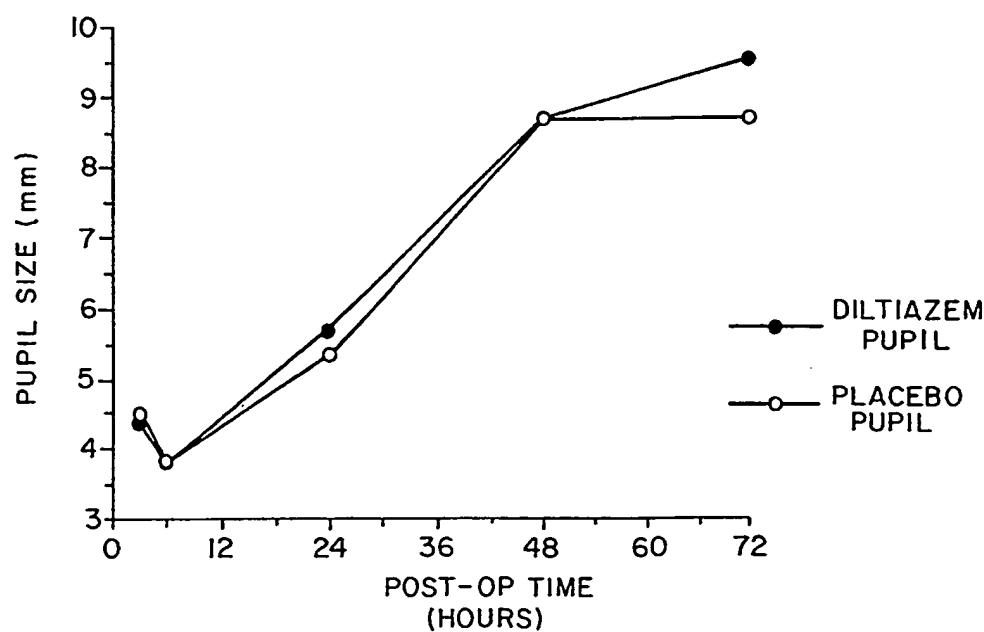


Fig. 3

Fig. 4
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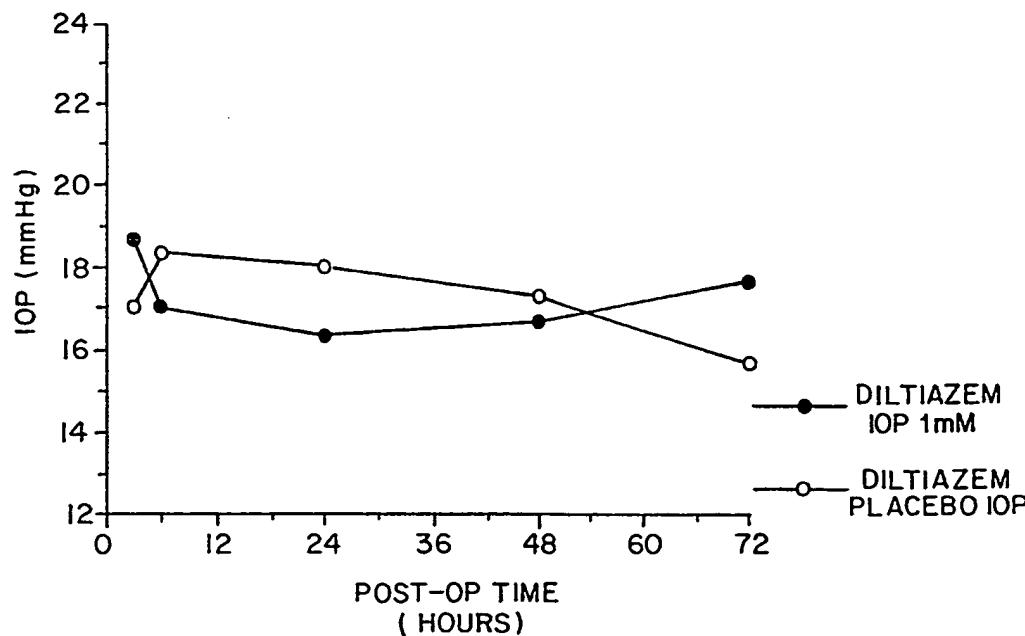


Fig. 5

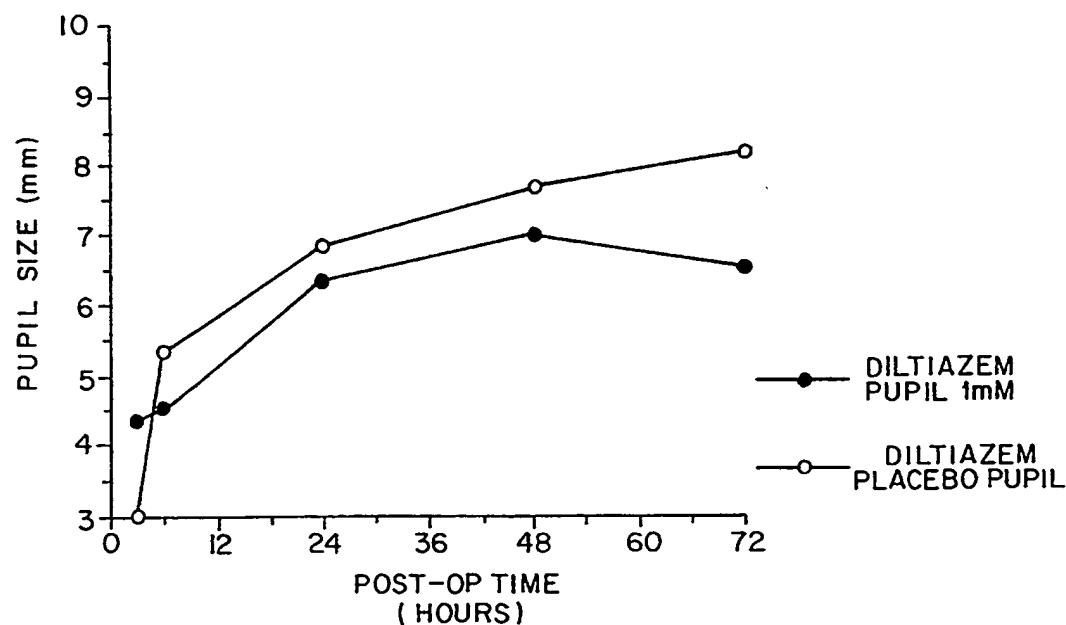


Fig. 6

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/07526

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135 A61K31/275 A61K31/44 A61K31/445 A61K31/495 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 04008 (UNIVERSIDAD DE ALICANTE) 19 March 1992 see page 15 - page 16; example 6	17-20
Y	see page 17, line 14 - line 15 ---	1-16
X	PHARMACOLOGY, BIOCHEMISTRY & BEHAVIOR, vol. 24, 1986 pages 329-331, BELESLIN D.B. ET AL 'Verapamil-Induced Behavioral, Autonomic and Motor Effects in Cats' see page 329, right column, line 9 - line 10	17-20
Y	see abstract ---	1-16
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

Date of mailing of the international search report

27 September 1995

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	'Rote Liste' 1993 , EDITIO CANTOR , AULENDORF/WURTT. see example 26104 see example 26119 see example 26124 -----	10-20
X	FR,A,2 593 395 (CORBIERE) 31 July 1987 see page 4 - page 5; examples I-V -----	10-20
E	WO,A,95 15958 (ALCON LAB.) 15 June 1995 see page 43, line 14 - page 44, line 6 see page 69, line 1 - line 16 -----	10-14, 17-19
A	EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 209, no. 3, 1991 pages 175-183, ANDERSSON S.E. ET AL 'Ruthenium Red and Capsicain Induce a Neurogenic Inflammatory Response in the Rabbit Eye: Effects of Conotoxin GVIA and Tetrodotoxin' cited in the application see page 181, right column, line 10 - line 13 -----	1-20

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INTERNATIONAL SEARCH REPORT

Internatio	Application No
PCT/US 95/07526	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9204008	19-03-92	AU-A-	8397191	30-03-92
		CA-A-	2073003	08-03-92
		EP-A-	0502143	09-09-92
FR-A-2593395	31-07-87	NONE		
WO-A-9515958	15-06-95	AU-B-	1336895	27-06-95